Primary hrHPV testing in cervical screening: the arguments

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Chapter 11

Summary and General Discussion

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11. General Discussion

Here we will discuss our findings as presented in the preceding chapters in relation to possible implementation of hrHPV testing in primary cervical screening

11.1 HrHPV testing detects clinically relevant ≥CIN2 lesions

In 1997, at the time the POBASCAM trial was initiated, we knew from relatively small pilot studies that hrHPV testing had a higher sensitivity and negative predictive value for the detection of ≥CIN2 lesions than cytology, at the cost of a slightly lower specificity (1). This result has been confirmed by others and by us (Chapter 2) (2-6).

It was however, still unknown whether the additionally detected lesions by hrHPV testing were clinically relevant, *i.e.*, whether it concerned non-regressing lesions. Several randomised controlled trials involving thousands of women are presently still ongoing with the objective to answer this question and to assess the long-term impact of hrHPV testing. These trials assess the effectiveness of primary screening by only hrHPV testing or by hrHPV testing in combination with cytology compared to screening by conventional or liquid-based cytology (Finland-Finnish Randomised Public Health Trial N=14,149, age 30-60 years; Italy-NTCC, N=33,364, age 35-60 years; UK-ARTISTIC N=19,344, age 30-64 years; Sweden-SWEDESCREEN N=12,527, age 32-38 years; Canada-CCCaST Canada, N=9,667, age 30-69 years; The Netherlands-POBASCAM N=49,220, age 29-61 years; The Netherlands-VUSA-screen N=50,000, age 30-60 years (7-13)).

In our publication concerning five years follow-up over two screening rounds of 17,155 women in the POBASCAM trial (Chapter 10) our data indicate that the earlier detected lesions by combined hrHPV and cytology screening are not a subset of regressive lesions but indeed clinically relevant lesions. This assumption is based on the notion that over two screening rounds, both in the intervention and control group of the POBASCAM trial the same number of ≥CIN2 lesions were detected. However, in the intervention group (women screened by hrHPV testing and cytology), many lesions were detected earlier, i.e., in the first screening round 56% more ≥CIN2 lesions compared to only cytology screening, and in the second round 47% less ≥CIN2 lesions. A preliminary cost-effectiveness analyses indicates that this earlier detection of ≥CIN2 leads to a larger reduction in the incidence and mortality of cervical cancer than cytology (14). The 5-years cumulative risk of ≥CIN2 after a combined negative hrHPV and cytology test result was reduced by 64%, compared to the risk after normal cytology only. These results could permit an extension of the screening interval by at least 1year. Since the risk after a negative hrHPV test result only was similar to the risk after a combined negative test result, the cost-effectiveness of adding cytological testing to hrHPV test is thus doubtful. After the 5-year follow-up data of the POBASCAM trial have been published, the greater sensitivity for the detection of ≥CIN2 by hrHPV testing as compared with cytology has been confirmed in population-based trial data by the Canadian trial (15) and our results concerning the detection of clinically relevant ≥CIN2 lesions have been confirmed by the Swedish trial (16).

Hence, screening by combined hrHPV testing and cytology results in an earlier detection of clinically relevant ≥CIN2 lesions. Earlier detection of such lesions and a strongly reduced five-year risk of ≥CIN2 could permit an extension of the screening interval.

11.2 HrHPV and attendance rate

We have shown that adding hrHPV testing to cervical screening does not decrease participation rates (Chapter 4), provided that 1) the general practitioners and other healthcare providers are well trained, and 2) the women concerned are informed regarding hrHPV. In the POBASCAM trial the training consisted of postgraduate courses for the general practitioners on hrHPV and its relationship with cervical cancer, and a leaflet for women invited to cervical screening with information on the nature of hrHPV infections, the lifetime prevalence, the clearance rate, and the increased risk for cervical cancer.

Before initiating the POBASCAM trial, a survey conducted among 1551 Dutch women indicated that hrHPV testing would not interfere with participation in cervical screening (17). Thus, the concern about the influence of hrHPV testing on the attendance rate in cervical screening because of the perceived association of cervical cancer with sexually transmitted infections (18;19) has been refuted by the attendance of the women in the POBASCAM trial. Furthermore, it has been shown that 34.2% of the women not attending cervical screening by cytology who were offered a self-sampling device for hrHPV testing did respond, thereby leading to a true increase in the attendance rate, which could not be obtained by a repeated invitation for cytology screening (20).

Hence, our experience is that implementation of hrHPV testing to the regular screening programme is well accepted, without a decrease in participation rate if attention is paid to the nature of information regarding hrHPV given to the women to be screened and especially to general practitioners and other health care providers.

11.3 The hrHPV test to be used in primary cervical screening

Which hrHPV test should be used in case of the implementing hrHPV testing in cervical screening? Currently, there are only two tests that have been extensively analysed for their performance and can be considered clinically validated, *i.e.*, the GP5+/6+ PCR and Hybrid Capture 2 (HC2) assays (6;21). These assays have a similar sensitivity and specificity when used for the detection of ≥CIN2 lesions (Chapter 9). The HC2 rapid capture system (RCS) allows high-throughput population screening in an automated format. The GP5+/6+ PCR-EIA assay has the advantage that direct genotyping is possible on the hrHPV-specific PCR products(22). Both HC2 and GP5+/6+ PCR show good to excellent intra- and inter-laboratory reproducibility (23-25).

The hrHPV test to be used in screening should display a good balance between sensitivity and specificity for the detection of ≥CIN2. Especially in cervical screening, tests with a lower specificity for ≥CIN2 lesions in favour of a very high sensitivity for hrHPV should not be used (25-27). Therefore, it is essential that hrHPV test requirements should be incorporated into the guidelines of the screening programme (25;28). Recently in The Netherlands, the general requirements for an hrHPV test to be used in screening have been formulated, including a good sensitivity for ≥CIN2, a high intra- and inter-laboratory reproducibility, and clinical validation (24).

As mentioned above, the GP5+/6+ PCR-EIA and the Hybrid Capture 2 tests are the only two clinically validated hrHPV tests that currently suit the general requirements for usage in cervical screening.

11.4 Risk management and HPV genotyping

Women with a prevalent hrHPV infection have an increased risk of cervical carcinoma. The odds ratio for cervical cancer associated with the presence of any hrHPV type was even 158.2 (95%CI 113.4 to 220.6) in a pooled analysis of 11 case-control studies conducted by the IARC in 11 countries involving 5000 women (21).

A full cost-effective analysis is essential to determine whether primary hrHPV testing alone is the preferred strategy for cervical screening. The following screening algorithm is one of the possibilities for the risk management of hrHPV positive women. With primary cervical screening by hrHPV testing we expect about 5% of the women aged 30-60 years to have a prevalent hrHPV infection (Chapter 3). Since cytology is a very good tool for risk stratification among hrHPV positive women, hrHPV-positive samples should be subjected to reflex cytology (*i.e.* cytology using the residual cells of the hrHPV sample). About 30% of the hrHPV-positive samples, *i.e,* 1.5% of the screened population, will have abnormal cytology. These women should be referred for colposcopy because of the very high risk of ≥CIN2 (risk of ≥CIN2, after BMD 33% 95%CI 28-38, after >BMD 79% 95%CI 74-83).

Because of the increased risk of developing ≥CIN2 lesions among the remainder 3.5% of women with a positive hrHPV test and normal cytology, these women should be recalled earlier than the next screening round, (5 year). We showed that repeat cytology and hrHPV testing (Chapter 7) and HPV genotyping (Chapter 5-8) can be used for risk stratification of these women with normal cytology. To illustrate the difference in risk of ≥CIN2 for different hrHPV types: women with normal cytology and HPV16/18 had a cumulative 18-month risk for ≥CIN2 of 25% whereas the risk for women infected with other hrHPV types was 5.3% (Chapter 7).

Based on the data as described in the previous chapters, cost-effectiveness analysis is presently being performed, to determine the optimal screening algorithm for cervical screening using hrHPV testing, including issues such as screening interval, starting age, and how cytology and HPV genotyping can be used for an effective follow-up of hrHPV positive women. An example of such a possible algorithm is shown in Figure 1.

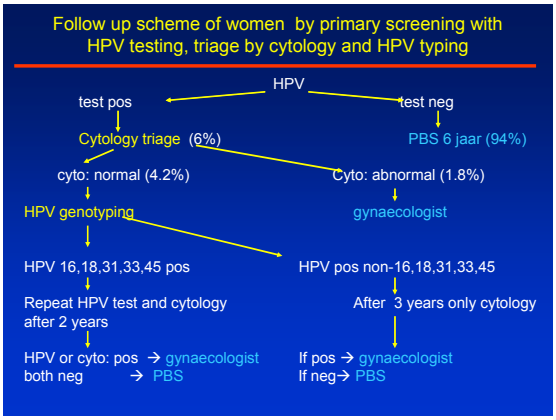

Figure 1: Possible follow-up scheme for hrHPV-positive women participating in cervical screening by primary HPV testing using cytology and hrHPV genotyping as triage tests.

11.5 Future developments: HPV vaccination

Use of HPV vaccines might have an impact as a preventive strategy for cervical cancer. Two HPV vaccines, Cervarix® and Gardasil®, are commercially available in The Netherlands. These vaccines induce high titers of neutralising antibodies, preventing infection of cervical epithelial cells by HPV types present in the vaccine. The vaccines have high efficacy against HPV16/18 related ≥CIN2 in women negative for HPV16/18 DNA at the time of vaccination (29;30). Therefore vaccination before sexarche (9-14 year) is the most optimal time for vaccination. The prophylactic vaccination with only HPV16 and HPV18 has the potential to protect against ~75% of the cervical

cancer cases since 70% of the cervical carcinomas is attributed to HPV16 or HPV18, and 5% protection can result from the cross-protection against HPV31 and HPV45 (29;30). The vaccines do not have a therapeutic effect on pre-existing HPV16/18 infections, nor pre-existing CIN lesions caused by these types.

From a public-health point of view and in order to maximise the preventive effect of vaccination, a high coverage of prepubertal women should be obtained. This outcome can be achieved by incorporation of HPV vaccines into existing national vaccination programmes offered to prepubertal women. The question can be asked whether cervical screening in the era of prophylactic vaccination will still be necessary. Since prophylactic vaccination of prepubertal women potentially prevents against 75% of cervical carcinomas and many women of the present generation of adult women are not vaccinated cervical screening will still remain. It can be expected that hrHPV testing rather than cytology will be the primary screening tool in the near future (31)

11.6 Conclusion

In this thesis we present definite proof that primary cervical screening by hrHPV testing detects clinically relevant ≥CIN2 lesions earlier than cytology, and does not lead to detection of a subset of regressive CIN lesions. The earlier detection of clinically relevant CIN lesions and the 64% reduced risk for ≥CIN2 lesions after a negative hrHPV test after 5 years compared to normal cytology, could permit extension of the current screening interval. This would be advantageous to women because of the reduction in the life-time number of screening test and referrals. This may result in an increased attendance to the screening programme. Since earlier detection of ≥CIN2 leads to a reduction in person years at risk in which ≥CIN2 lesions can progress to cervical cancer, the earlier diagnoses of ≥CIN2 might lead to a reduction in cervical cancer (14;15). Provided that all parties involved in screening, especially the general practitioners, are supplied with adequate information about hrHPV, primary cervical screening by hrHPV is well accepted and does not lead to a decrease in attendance (chapter 4). HrHPV tests to be used in primary cervical screening should display an optimal balance between sensitivity and specificity for the detection of ≥CIN2 and test requirements should be incorporated in screening guidelines. Test requirements have recently been formulated by Hesselink (25). Currently, two tests, i.e., GP5+/6+ PCR EIA and HC2 are clinically validated and can be used as primary screening tools. A full cost-effective analysis is presently performed on the basis of our data to determine which algorithm for hrHPV testing should be used. In addition, cytology and HPV genotyping seem promising tests to further stratify hrHPV-positive women and model studies are ongoing to find out the most optimal, simple and women-friendly follow-up algorithm. It can be expected that in the future a molecular test will replace the triage by reflex cytology, thereby changing from a “subjective technique” to an “objective highly reproducible test”.

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